Complicated pregnancies in inherited distal renal tubular acidosis: importance of acid-base balance

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Abstract: Inherited distal renal tubular acidosis (dRTA) is caused by impaired urinary acid excretion resulting in hyperchloremic metabolic acidosis. Although the glomerular filtration rate (GFR) is usually preserved, and hypertension and overt proteinuria are absent, it has to be considered that patients with dRTA also suffer from chronic kidney disease (CKD) with an increased risk for adverse pregnancy-related outcomes. Typical complications of dRTA include severe hypokalemia leading to cardiac arrhythmias and paralysis, nephrolithiasis and nephrocalcinosis. Several physiologic changes occur in normal pregnancy including alterations in acid-base and electrolyte homeostasis as well as in GFR. However, data on pregnancy in women with inherited dRTA are scarce. We report the course of pregnancy in three women with hereditary dRTA. Complications observed were severe metabolic acidosis, profound hypokalemia aggravated by hyperemesis gravidarum, recurrent urinary tract infection (UTI) and ureteric obstruction leading to renal failure. However, the outcome of all five pregnancies (1 pregnancy each for mothers n. 1 and 2; 3 pregnancies for mother n. 3) was excellent due to timely interventions. Our findings highlight the importance of close nephrologic monitoring of women with inherited dRTA during pregnancy. In addition to routine assessment of creatinine and proteinuria, caregivers should especially focus on acid-base status, plasma potassium and urinary tract infections. Patients should be screened for renal obstruction in the case of typical symptoms, UTI or renal failure. Furthermore, genetic identification of the underlying mutation may (a) support early nephrologic referral during pregnancy and a better management of the affected woman, and (b) help to avoid delayed diagnosis and reduce complications in affected newborns.

DOI: https://doi.org/10.1007/s40620-016-0370-x

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Short title: Pregnancy in inherited dRTA

Word count abstract: 134

Word count manuscript: 1477

Acknowledgements

We thank our patients and appreciate the help of all family members who participated in this study. Particularly, we thank Dr. Rosa Vargas-Poussou for performing the genetic analysis and Dr. Giuseppina Spartà who initially diagnosed index patient 3 at the University Children's Hospital in Zurich.
The study was in part supported by the 7th EU Frame work project Eurenomics (to C.A. Wagner).

Conflict of interest

All authors have nothing to declare.

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Abstract

Inherited distal renal tubular acidosis (dRTA) is caused by impaired urinary acid excretion resulting in hyperchloremic metabolic acidosis. Although glomerular filtration rate is usually preserved, and hypertension and overt proteinuria are absent, it has to be considered that patients with dRTA also suffer from chronic kidney disease (CKD) with an increased risk for adverse pregnancy-related outcomes. Typical complications of dRTA include severe hypokalemia leading to cardiac arrhythmias and paralysis, nephrolithiasis and nephrocalcinosis. Several physiologic changes occur in normal pregnancy including alterations in acid base and electrolyte homeostasisas well as in GFR. However, data on pregnancy in women with inherited dRTA are scarce. We report the course of pregnancy in three women with hereditary dRTA. Complications observed were severe metabolic acidosis, profound hypokalemia aggravated by hyperemesis gravidarum, recurrent urinary tract infection and ureteric obstruction leading to renal failure. However, the outcome of all five pregnancies was excellent due to timely interventions. Our findings highlight the importance of close nephrologic monitoring of women with inherited dRTA during pregnancy. In addition to routine assessment of creatinine and proteinuria, caregivers should especially focus on acid base status, plasma potassium and urinary tract infections. Patients should be screened for renal obstruction in case of typical symptoms, UTI or renal failure. Furthermore, genetic identification of the underlying mutation may i) support early nephrologic referral during pregnancy and a better management of the affected woman and ii) help to avoid delayed diagnosis and reduce complications in affected newborns.

Keywords

AE1 mutation, B1 mutation, metabolic acidosis, hypokalemia, hyperemesis gravidarum

Introduction

Distal renal tubular acidosis (dRTA) refers to a group of tubular disorders causing disturbances in acid-base homeostasis and is characterized by defective urinary acid excretion resulting in hyperchloremic metabolic acidosis with inappropriate alkaline urine[1]. dRTA is either inherited, acquired or idiopathic. Mutations in three different genes have been implicated in hereditary autosomal recessive or dominant dRTA, namely *SLC4A1, ATP6V1B1*, and *ATP6V0A4*[1]. In recessive forms, clinical manifestation usually occurs during early infancy or childhood and includes failure to thrive, dehydration, nephrocalcinosis, and rickets. In dominant forms, clinical

manifestation typically occurs in young adults and includes nephrolithiasis and osteoporosis or osteomalacia. Other major complications include severe hypokalemia resulting in paralysis, rhabdomyolysis or life-threatening arrhythmia[2,3]. Therapy includes lifetime treatment with potassium citrate and/or sodium bicarbonate to prevent growth retardation in children, kidney stone formation, and progression of nephrocalcinosis.

It has been reported that female CKD patients are at increased risk for complications during pregnancy and therefore close interdisciplinary monitoring is essential in this vulnerable population[4-6]. However, individuals with tubulopathies such as dRTA usually have a preserved eGFR and thus are often not perceived as CKD patients. Subsequently, monitoring and treatment during pregnancy may be insufficient. By now, no systematic data exist on the course of pregnancy in hereditary dRTA affected mothers and both, mother and child outcome. Single case reports have reported pregnancy in several types of RTA (proximal, distal, inherited, secondary) to be predominantly complicated by hypokalemia[7-9] or hypertension[10]. Here, we report a series of three women with inherited dRTA developing several complications during pregnancy.

Case 1

The 30-year-old woman was diagnosed with dRTA at 4 months because of failure to thrive and vomiting[11]. She also suffered from sensorineural hearing loss (SNHL) and hearing aids were introduced at the age of 3.5 years (Table 1). She had a history of bilateral nephrocalcinosis and a non-functioning left kidney due to vesicoureteral reflux. Estimated glomerular filtration rate (eGFR) has been stable in the normal range since she was diagnosed with dRTA. Her long-term medication consisted of potassium citrate (20 mEq tid) and sodium bicarbonate (1000 mg tid). At age 29 she became pregnant for the first time. The gestation period was complicated by severe urinary tract infections (UTI) and pyelonephritis requiring repeated antibiotic treatment. Further, she developed urinary tract obstruction and was subjected to right-sided ureteric stenting and subsequent antibiotic prophylaxis during the second and third trimenon (Table 1). Patients with nephrocalcinosis are more prone to develop UTIs[12]. Since the obstruction in our patient occurred early in the second trimenon she did not undergo CT scan to distinguish between a ureteric calculus or an inflammatory stricture, therefore the etiology remained unclear. Our patient reported regular intake and good tolerance of potassium citrate and sodium bicarbonate during the whole period of pregnancy. However, she developed hypokalemia and low bicarbonate levels during pregnancy (Table 1), that may be caused by either a higher demand of alkali supplementation during pregnancy or malcompliance. At term she delivered a healthy female newborn by cesarean section. Postnatal investigation of the newborn showed no abnormalities (Table 2).

Case 2

The 26-year-old woman was hospitalized in Zagreb at the age of 12 months where she was diagnosed with dRTA and SNHL (Table 1)[11]. Her eGFR has always been in the normal range and no kidney stones or UTIs were observed. However, her first pregnancy at the age of 22 was complicated by hypokalemia and aggravation of metabolic acidosis especially during the first trimenon because of discontinuation of potassium citrate (2500 mg tid) due to hyperemesis gravidarum. In addition, the patient had not restarted potassium citrate after the first trimenon since she was afraid of her sickness to recur. Rescue therapy with e.g. intravenous alkali supplementation could not be applied because the patient was referred to her nephrologist after all complaints had already ceased. Fortunately, the prenatal course was otherwise uneventful. She delivered a healthy male infant by cesarean section at term (Table 2). To date, pediatric follow-up showed normal development.

Case 3

The 32-year-old woman, who was expecting her third child after having two healthy children and one miscarriage (gravida 4, para 3), had been diagnosed with dRTA at the age of 18 months. Subsequently she was supplemented with potassium citrate and sodium bicarbonate. As expected she developed nephrocalcinosis and osteopenia but no hearing abnormalities. Estimated glomerular filtration rate was slighty reduced since 2011 with an eGFR below 90 ml/min (Table 1). Her first pregnancy was in 2008 and was terminated by curettage because of a missed abortion. Second and third pregnancies required hospital admission because of severe muscular weakness and profound hypokalemia (serum potassium <2 mmol/l). Additionally, she had recurrent episodes of flank pain due to hydronephrosis at 30 weeks gestation during her third pregnancy. Both pregnancies ended uneventfully by vaginal delivery of two healthy girls (Table 2). In 2014, during the fourth pregnancy she repeatedly developed symptomatic hypokalemia and decompensated metabolic acidosis after stopping potassium citrate because of hyperemesis. In addition, liver function parameters were elevated in the last trimenon suspicious of preeclampsia or HELLP (hemolysis, elevated liver, low platelet) syndrome and labour was induced 3 weeks before due date. Also this time she had an uncomplicated delivery of a female newborn by vaginal route. Notably, this patient was not regularly seen by a nephrologist during her former pregnancies and no genetic testing had been performed yet. During her fourth pregnancy, she was treated by a new nephrologist who contacted us as a tertiary care center to guide therapy and further diagnostic procedures. After delivery, genetic analysis of the mother was performed in a laboratory with long-standing expertise in tubulopathies and revealed a heterozygous mutation in the *SLC4A1* gene (c.1766G>A, p.Arg589His) (Table 1). Based on the dominant inheritance pattern genetic analysis was consequently performed in all three children and the same mutation was

detected in the last-born child (Table 2). This 18-months-old infant is suffering from failure to thrive, nephrocalcinosis and metabolic acidosis (Table 2).

Discussion

Distal renal tubular acidosis is a tubular disorder defined by normal anion gap metabolic acidosis and inappropriate alkaline urine, both caused by the reduced capacity of the kidneys to excrete ammonium and acids[1]. Mutations in three different genes have been so far implicated in dRTA, namely *SLC4A1, ATP6V1B1*, and *ATP6V0A4*, all encoding for proteins that are expressed in the acid-secretory cells of the collecting duct and play a crucial role in distal urine acid excretion[1]. *SLC4A1* mutations are mostly inherited in an autosomal dominant manner and have a high prevalence in some Southeast Asian countries, where the disease is predominantly caused by recessive mutations[13]. Some patients with recessive *SLC4A1* mutations may develop hemolytic disease such as Southeast Asian Ovalocytosis[13]. Interestingly, most patients with recessive mutations present either with dRTA or hemolytic disease, and only in rare instances with a combination of both phenotypes[1]. The p.Arg589His mutation is among the most common *SLC4A1* mutations in autosomal dominant dRTA as also detected in our patient[14]. *ATP6V1B1* and *ATP6V0A4* are two different subunits of the vacuolar H^+-ATPase and mutations are inherited in an autosomal recessive manner. Heterozygous mutations may underlie forms of incomplete dRTA[15]. Affected individuals with recessive dRTA are usually diagnosed during infancy or childhood presenting with failure to thrive and rickets resulting from profound hyperchloremic metabolic acidosis[16,17]. Further, patients present with nephrolithiasis and/or nephrocalcinosis, hearing abnormalities (SNHL), and occasionally abnormal widening of the vestibular aqueduct[11]. Rarely patients develop chronic renal failure that may result from progressive nephrocalcinosis but the underlying pathomechanisms are not completely understood. Other serious complications such as severe hypokalemia resulting in paralysis, rhabdomyolysis, or life-threatening arrhythmia are frequently reported highlighting the importance of lifelong alkali treatment with potassium citrate and/or sodium bicarbonate[2,3]. Alkali therapy is also aimed to prevent growth retardation in children, kidney stone formation, bone disease and progression of nephrocalcinosis, although adherence to therapy is often attenuated because of gastrointestinal side effects of potassium citrate. Unfortunately, there is no benefit of alkali therapy on hearing abnormalities[16]. eGFR is usually preserved in individuals with dRTA, however, they suffer from CKD due to tubular dysfunction[18] and are at high risk for adverse pregnancy-related outcomes[4-6]. Precisely because of normal eGFR and lack of albuminuria, caregivers/gynecologists/obstetricians may overlook other typical complications during pregnancy such as

severe hypokalemia and worsening of metabolic acidosis and underestimate the importance of early nephrologic referral and the need for interdisciplinary management of pregnant women with dRTA.

To date, little is known about the impact of inherited forms of dRTA on pregnancy including mother and child outcome Several physiologic changes concerning kidney function occur during pregnancy such as increase in glomerular filtration rate[19]. Respiratory alkalosis with subsequent increased renal bicarbonate excretion is the main acid-base alteration in pregnancy[20]. Under normal conditions both mother and fetus adapt well to the fall in pCO_2 and bicarbonate. However, maternal acidosis as reported in our patient series may have several unfavorable effects on the fetus if untreated or diagnosis is delayed[20,21]. First, oxygen supply via the placenta may be attenuated due to vasoconstriction of uterine vessels causing fetal distress[7,21]. Second, maternal metabolic acidosis may impair fetal bone growth and development[7,8]. Two of our patients suffered from severe hyperemesis gravidarum and temporarily stopped alkali supplementation resulting in exacerbation of the metabolic acidosis and profound hypokalemia. Furthermore, lower plasma bicarbonate may also be explained by increased filtration of bicarbonate as a consequence of pregnancy-related increase in eGFR[19]. However, both hypokalemia and decrease in serum bicarbonate were also present in our first case who apparently continued her alkali treatment suggesting that patients with dRTA may require higher doses of potassium and alkali therapy during pregnancy. This has also been observed by others[8]. Additionally, severe hypokalemia may result in paralysis and eventually rhabdomyolysis as reported in several case reports of pregnant women with RTA. This was not observed in our patients potentially due to close monitoring and timely treatment[7,9]. One of our patients was additionally suffering from recurrent UTI and obstruction requiring long-term antibiotic treatment and ureteric stenting. Nephrocalcinosis and kidney stones as typical clinical findings in these patients may increase the risk of UTI in pregnant dRTA patients in addition to general physiologic changes of the urinary tract during pregnancy therefore predisposing pregnant women to UTI including pyelonephritis. In contrast to Rowe et al. none of our patients developed hypertension during pregnancy and kidney function remained stable post-partum[10]. Fortunately, all deliveries were uneventful with healthy term neonates as reported in the literature[7-10] suggesting no adverse impact on child outcome in RTA patients.

In our case series, case 1 and 2 had been genetically tested before pregnancy and subsequently subjected to genetic counseling. Case 3 was referred to our center after having 3 children and genetic testing was initiated by us after her third delivery. Unfortunately no genetic counseling was provided to this patient before pregnancy. In our opinion, genetic testing is strongly recommended in all pregnant women with inherited dRTA and unknown underlying mutation to provide pre- or at least post-conceptional counseling and to avoid delayed diagnosis and treatment in potentially affected infants, particularly in patients with the autosomal dominant form and in

consanguineous couples. The analysis should be performed in laboratories with expertise on renal tubular diseases. Additionally, early nephrologic referral and interdisciplinary management are inevitable in pregnant women with clinically diagnosed or suspected inherited dRTA.

In conclusion, women with inherited dRTA are at high risk to develop hypokalemia and exacerbation of metabolic acidosis during pregnancy. Additionally, they are predisposed to UTI and other urologic complications. Thus, in addition to regular monitoring of creatinine and proteinuria as for all women with CKD, in particular close monitoring of acid-base (assessed by blood gas analysis) and electrolyte status (including sodium, potassium, chloride, and magnesium) is required to prevent life-threatening hypokalemia and decompensation of metabolic acidosis. Further, affected individuals should be thoroughly screened for UTI or obstruction if deterioration of renal function occurs. Additionally, we recommend early nephrologic referral and interdisciplinary management for all pregnant women with clinically diagnosed or suspected dRTA. Finally, timely genetic testing should be performed to provide pre- or post-conceptional counseling to affected women and early diagnosis, identification and treatment of complications in affected newborns.

Informed Consent

Written informed consent was obtained from all patients for publication.

References

1. Wagner CA, Devuyst O, Bourgeois S, Mohebbi N. Regulated acid-base transport in the collecting duct. *Pflugers Archiv : European journal of physiology.* May 2009;458(1):137-156.

2. Sengul E, Bunul F, Yazici A, et al. An Unusual Initial Presentation of Sjogren's Syndrome: Severe Hypokalemic Paralysis Secondary to Distal Renal Tubular Acidosis. *The Eurasian journal of medicine.* Oct 2013;45(3):218-221.

3. van den Wildenberg MJ, Hoorn EJ, Mohebbi N, et al. Distal renal tubular acidosis with multiorgan autoimmunity: a case report. *American journal of kidney diseases : the official journal of the National Kidney Foundation.* Apr 2015;65(4):607-610.

4. Cabiddu G, Castellino S, Gernone G, et al. A best practice position statement on pregnancy in chronic kidney disease: the Italian Study Group on Kidney and Pregnancy. *Journal of nephrology.* Jun 2016;29(3):277-303.

5. Alsuwaida A, Mousa D, Al-Harbi A, Alghonaim M, Ghareeb S, Alrukhaimi MN. Impact of early chronic kidney disease on maternal and fetal outcomes of pregnancy. *The journal of maternal-fetal & neonatal medicine : the official journal of the European Association of Perinatal Medicine, the Federation of Asia and Oceania Perinatal Societies, the International Society of Perinatal Obstet.* Dec 2011;24(12):1432-1436.

6. Piccoli GB, Cabiddu G, Attini R, et al. Risk of Adverse Pregnancy Outcomes in Women with CKD. *Journal of the American Society of Nephrology : JASN.* Aug 2015;26(8):2011-2022.

7. Firmin CJ, Kruger TF, Davids R. Proximal renal tubular acidosis in pregnancy. A case report and literature review. *Gynecologic and obstetric investigation.* 2007;63(1):39-44.

8. Hardardottir H, Lahiri T, Egan JF. Renal tubular acidosis in pregnancy: case report and literature review. *The Journal of maternal-fetal medicine.* Jan-Feb 1997;6(1):16-20.

9. Srisuttayasathien M. Hypokalemia-Induced Rhabdomyolysis as a result of Distal Renal Tubular Acidosis in a Pregnant Woman: A Case Report and Literature Review. *Case reports in obstetrics and gynecology.* 2015;2015:947617.

10. Rowe TF, Magee K, Cunningham FG. Pregnancy and renal tubular acidosis. *American journal of perinatology.* 1999;16(4):189-191.

11. Mohebbi N, Vargas-Poussou R, Hegemann SC, et al. Homozygous and compound heterozygous mutations in the ATP6V1B1 gene in patients with renal tubular acidosis and sensorineural hearing loss. *Clinical genetics.* Mar 2013;83(3):274-278.

12. Piccoli GB, Attini R, De Pascale A, et al. Protean presentation and multiple challenges of nephrocalcinosis in pregnancy (six pregnancies in four patients). *Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association.* Mar 2012;27(3):1131-1138.

13. Khositseth S, Bruce LJ, Walsh SB, et al. Tropical distal renal tubular acidosis: clinical and epidemiological studies in 78 patients. *QJM : monthly journal of the Association of Physicians.* Sep 2012;105(9):861-877.

14. Alper SL. Familial renal tubular acidosis. *Journal of nephrology.* Nov-Dec 2010;23 Suppl 16:S57-76.

15. Dhayat NA, Schaller A, Albano G, et al. The Vacuolar H+-ATPase B1 Subunit Polymorphism p.E161K Associates with Impaired Urinary Acidification in Recurrent Stone Formers. *Journal of the American Society of Nephrology : JASN.* May 2016;27(5):1544-1554.

16. Vargas-Poussou R, Houillier P, Le Pottier N, et al. Genetic investigation of autosomal recessive distal renal tubular acidosis: evidence for early sensorineural hearing loss associated with mutations in the ATP6V0A4 gene. *Journal of the American Society of Nephrology : JASN.* May 2006;17(5):1437-1443.

17. Stover EH, Borthwick KJ, Bavalia C, et al. Novel ATP6V1B1 and ATP6V0A4 mutations in autosomal recessive distal renal tubular acidosis with new evidence for hearing loss. *Journal of medical genetics.* Nov 2002;39(11):796-803.

18. Kidney Disease: Improving Global Outcomes (KDIGO) CKD Work Group. KDIGO 2012 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. *Kidney inter., Suppl.* 2013;3:1-150.
19. Davison JM, Dunlop W. Renal hemodynamics and tubular function normal human pregnancy. *Kidney international.* Aug 1980;18(2):152-161.
20. Blechner JN. Maternal-fetal acid-base physiology. *Clinical obstetrics and gynecology.* Mar 1993;36(1):3-12.
21. Omo-Aghoja L. Maternal and fetal Acid-base chemistry: a major determinant of perinatal outcome. *Annals of medical and health sciences research.* Jan 2014;4(1):8-17.

Table 1. Clinical and laboratory characteristics of the patients

	Mother 1			Mother 2			Mother 3		
Age at diagnosis	4 months			12 months			18 months		
Nephrocalcinosis	y			y			y		
SNHL	y			y			n		
Age at current pregnancy	30			22			31		
No of Pregnancies	1			1			4		
No of children	1			1			3		
No of children affected	0			0			1		
Gene	*ATP6V1B1*			*ATP6V1B1*			*SLC4A1*		
Mutation	c.242T>C, p.Leu81Pro c.481G>A, p.Glu161Lys (double homozygous)			c.242T>C, p.Leu81Pro c.1037C>G, p.Pro346Arg (compound hetereozygous)			c.1766G>A, p.Arg589His		
Inheritance	recessive			recessive			dominant		
Laboratory parameters	Before pregnancy	During pregnancy	After pregnancy	Before pregnancy	During pregnancy	After pregnancy	Before pregnancy	During pregnancy	After pregnancy
Potassium, mmol/l	3.6	3.0	3.5	3.6	3.3	3.6	4.3	2.1	3.5
Creatinine, umol/l	72	68	73	63	48	67	100	108	125
eGFR (CKD-EPI), ml/min	98	104	96	121	134	111	66	60	50
Change of eGFR in % of baseline eGFR	-	+5.8	-2.0	-	+10.7	-8.3	-	-9.1	-24.2
Blood pH	7.35	7.36	7.44	7.35	7.43	7.35	7.37	7.27	7.25
Bicarbonate, mmol/l	23	15	25	28	21	24	24	11	19
Plasma anion gap	8.0	9.7	n.d.	8.4	6.3	8.0	n.d.	9.0	n.d.
Plasma lactate	2.0	1.5	n.d.	1.2	1.7	0.7	n.d.	0.6	n.d.

Chloride, mmol/l	108	113	n.d.	105	108	109	n.d.	120	n.d.
Urine pH	7.5	8.0	8.5	8.0	8.0	7.5	8.0	7.0	7.0
Hemoglobin, g/l	131	128	107	138	115	136	125	143	124
Polyhydramnios	-	n	-	-	n	-	-	n	-
Kidney stones	n	n	n	n	n	n	n	n	n
UTI	sporadic	y	n	n	Asymptomatic leukocyturia	n	y	y	n
Obstruction	n	y (ureteric stenting)	n	n	n	n	n	y	n
Treatment	Potassium citrate, sodium bicarbonate			Potassium citrate			Potassium citrate, sodium bicarbonate		

y: yes, n: no, n.d.: not determined, SNHL: sensorineural hearing loss , UTI: urinary tract infection

Table 2. Laboratory and clinical data of the children

	1st Child of mother 1	1st Child of mother 2	1st Child of mother 3	2nd child of mother 3	3rd Child of mother 3
Gestational age at birth	38+2	38+4	40+2	38+5	37+3
Gender	female	male	female	female	female
Mode of delivery	elective cesarean section	elective cesarean section	vaginal	vaginal	vaginal
Birth weight, g	3280	3230	3130	2880	2790
Height, cm	47	50	52 (at 1 month)	47	46
Blood pH	7.41	7.33	7.41 (at 1 month)	7.30	7.36 (at 1 month)
Urine pH	6.0	n.d.	7.0 (at 4 months)	7.0 (at 1 year)	7.0
Nephrocalcinosis	n	n	n	n	y
Failure to thrive	n	n	n	n	y
Mutation	n.d.	n.d.	none	none	SLC4A1c.1766G>A, p.Arg589His

y: yes, n: no, n.d.: not determined, n/a: not available